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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :		(11) International Publication Number:	WO 99/00125
A61K 31/33, 31/70, C07D 267/00, C07H 5/04, 5/06, 17/08	A1	(43) International Publication Date:	7 January 1999 (07.01.99)

(21) International Application Number: PCT/US98/13061

(22) International Filing Date: 24 June 1998 (24.06.98)

(30) Priority Data:

60/051,115	27 June 1997 (27.06.97)	US
9800457.5	9 January 1998 (09.01.98)	GB

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(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

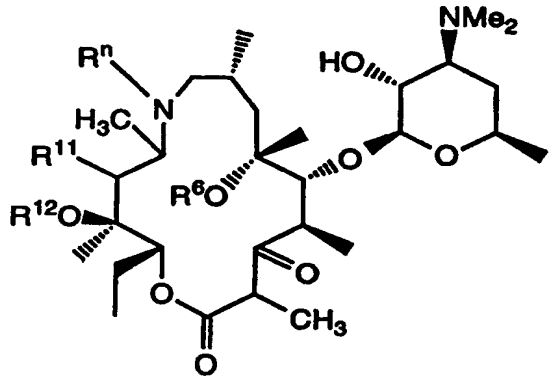
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: 9A–AZA–3–KETOLIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

(57) Abstract

Compounds are disclosed which are represented by formula (I) as well as salts and hydrates thereof. Pharmaceutical compositions and methods of treatment are also included.



(I)

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TITLE OF THE INVENTION

9A-AZA-3-KETOLIDES, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

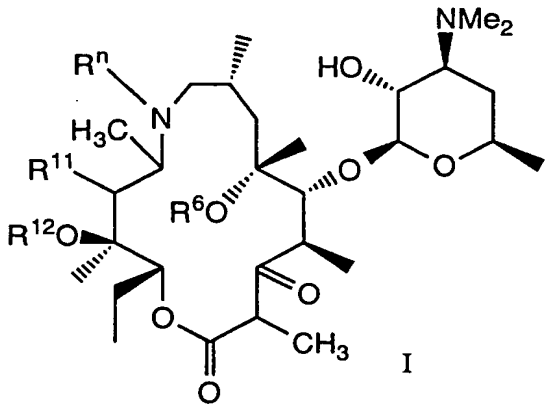
BACKGROUND OF THE INVENTION

The present invention relates to 9a-aza-3-ketolides, compositions containing such compounds and methods of use therefore. Azalides are structurally similar to erythromycin A, except for the presence of a ring nitrogen atom at the 9a-position. The compounds of the invention are further distinguished from erythromycins and erythromycin-like compounds in that the cladinose moiety has been cleaved from the molecule, and a carbonyl group is present at position 3.

The 9a-azalides of the present invention are potent antibiotics which are useful for the treatment of gram positive and gram negative organisms. As such the compounds find utility in human and veterinary medicine for the treatment of infections caused by susceptible organisms.

SUMMARY OF THE INVENTION

The present invention addresses a compound represented by formula I:



I

or a salt or hydrate thereof wherein:

R^{11} and R^{12} are taken separately or together;

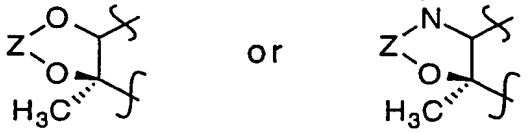
when taken separately, R^{11} is selected from the group consisting of: NR'R", $O(CH_2)_nAr$ and $S(CH_2)_nAr$;

and R^{12} represents a member selected from the group consisting of: H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, and $(CH_2)_nAr$ wherein

$(CH_2)_n$ is alkylene, in which n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

and Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 groups R^a which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

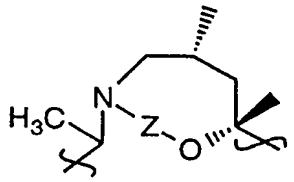
when taken together, R^{11} and R^{12} taken with the intervening atoms form an additional ring as shown in the following structure:



wherein R' and Z are as defined below;

R^n represents H, C_{1-6} alkyl, C_{1-6} alkyl interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined above, and R^6 represents CH_3,

or R^6 and R^n are taken in conjunction with the intervening atoms and form an additional ring as shown in the following structure:



Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2;

X represents CH_2 , CHF, CF_2, $C=CH_2$, CHSR, $CHCH_3$, C=S, C=O or CHOR;

R represents H, CS_2CH_3, phenyl, C_{1-6} alkyl or C_{1-6} alkyl interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

R^z represents C_{1-6} alkyl or phenyl;

R' is selected from H, C_{1-3} alkyl, NHR"and $(CH_2)_nAr$, and

R" represents H, C_{1-3} alkyl or $(CH_2)_nAr$.

Also included is a pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

Also included is a method of treating a bacterial infection in a mammalian patient in need of such treatment which is comprised of administering to said patient a compound of formula I in an amount which is effective for treating a bacterial infection.

DETAILED DESCRIPTION OF THE INVENTION

The invention is described in connection with the following definitions unless otherwise specified.

Alkyl refers to C1-6 straight or branched chain alkyl groups. The alkyl group can be uninterrupted or interrupted of O, $S(O)_y$ wherein y is 0, 1 or 2, N, NH, NCH_3 or C(O) as specified. When interrupted, a methylene spacer can be present which is adjacent to an interrupting moiety. Thus, this would include, for example, -CH_2-O-

and -O-CH_2-. When two or three of these interrupting groups is present, they may be separate or together. Me represents methyl.

Acyl refers to C_{1-5} alkyl-C(O)-.

When the group -$(CH_2)_n$Ar is present, the alkyl portion -$(CH_2)_n$ can be uninterrupted or interrupted as described above, with O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O). This includes groups where the interrupting atom is at either end of the chain. Thus, -C(O)-phenyl, -NH-phenyl, -C(O)NH-$(CH_2)_{1-10}$-phenyl, -CH_2-O-phenyl as well as like groups are included. Additionally, the alkylene portion can be substituted with 1-3 groups selected from R^a.

Each R^a is independently selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O).

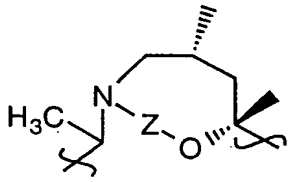
Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 groups selected from R^a which is halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a substituent groups are attached to Ar, said substituents may be taken in combination with any intervening atoms to represent a 5-6 membered aromatic or non-aromatic ring, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, NH, NCH_3 or C(O) wherein y is as previously defined. Examples of Ar and Ar substituted with 1-3 R^a groups include phenyl, naphthyl, quinolinyl, isoquinolinyl, pyridyl, imidazolyl, pyrrolyl, thiophenyl, benzothiazolyl, thiazolyl, furanyl, benzofuranyl, indolyl, fluorenonyl, dibenzofuranyl and naphthosultamyl.

Halo means Cl, F, Br or I.

A preferred aspect of the invention relates to compounds wherein R^n represents H, C_{1-6} alkyl, C1-6 alkyl substituted with 1-3 R^a groups or $(CH_2)_n$Ar. Within this subset of compounds all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^6 represents CH_3.

Another preferred aspect of the invention relates to compounds wherein R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:



in which Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined. Within this subset of compounds, all other variables are as originally defined.

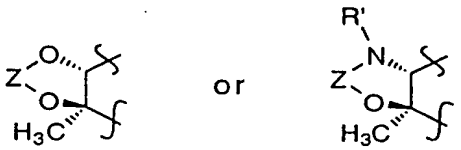
Another preferred aspect of the invention relates to compounds wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein $(CH_2)_nAr$ is present, and the alkylene chain is uninterrupted, and n is an integer of from 1-3. The alkylene group is either unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl. Within this subset, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^{11} and R^{12} are taken separately, and R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^{11} and R^{12} are taken separately, and R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar. Within this subset of compounds, all other variables are as originally defined.

Another preferred aspect of the invention relates to compounds wherein R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring as shown in the following structure:



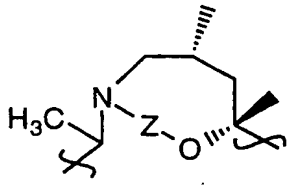
wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined. Within this subset of compounds, all other variables are as originally defined.

A preferred subset of compounds of the present relates to compounds wherein:

R^n represents H, C1-6 alkyl, C1-6 alkyl substituted with 1-3 R^a groups or $(CH_2)_nAr$;

R^6 represents H or CH_3;

or R^6 and R^n are taken together with the intervening atoms to form a ring as shown in the following structure:



in which Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined;

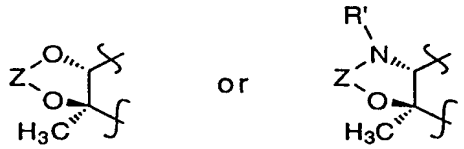
Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

$(CH_2)_n$ represents an alkylene chain which is uninterrupted, and n is an integer of from 1-3, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

R^{11} and R^{12} are taken separately, and R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined, and

R^{12} represents H, C1-6 alkyl or (CH2)n-Ar, or

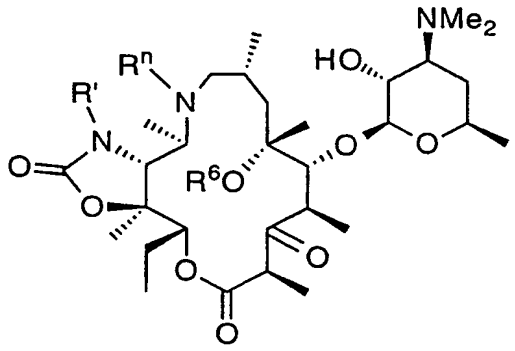
R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring as shown in the following structure:

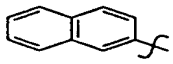
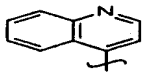
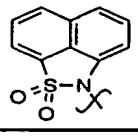
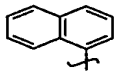
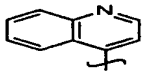
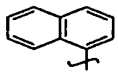


wherein Z is as originally defined.

Specific compounds which are included in the present invention are set forth below.

Table 1



#	Rn	R6	R'	Ar
1	CH_3	CH_3	$(CH_2)_4Ar$	
2	CH_3	CH_3	$(CH_2)_4Ar$	
3	CH_3	CH_3	$(CH_2)_5Ar$	
4	CH_3	CH_3	$(CH_2)_3Ar$	
5	CH_3	CH_3	$(CH_2)_4Ar$	
6	CH_3	CH_3	$(CH_2)_4Ar$	
7	---CH_2---		$(CH_2)_4Ar$	

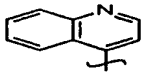
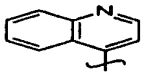
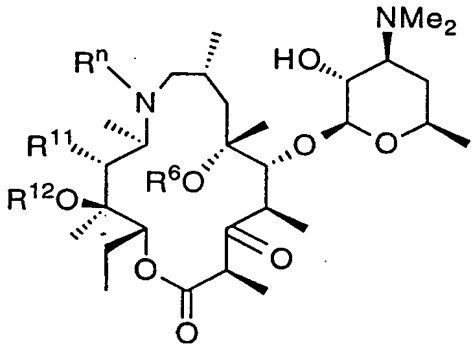
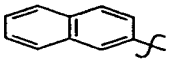
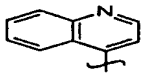
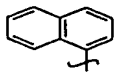
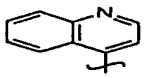
8	---CH_2---		$NH(CH_2)_3Ar$	
9	CH_3	CH_3	$NH(CH_2)_3Ar$	

Table 2



#	R^n	R^6	R^{11}	R^{12}	Ar
10	CH_3	CH_3	$O(CH_2)_3Ar$	H	
11	CH_3	CH_3	OH	$(CH_2)_3Ar$	
12	CH_3	CH_3	$O(CH_2)_3Ar$	H	
13	CH_3	CH_3	$O(CH_2)_4Ar$	H	
14	CH_3	CH_3	$S(CH_2)_4Ar$	H	

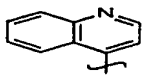
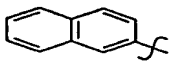
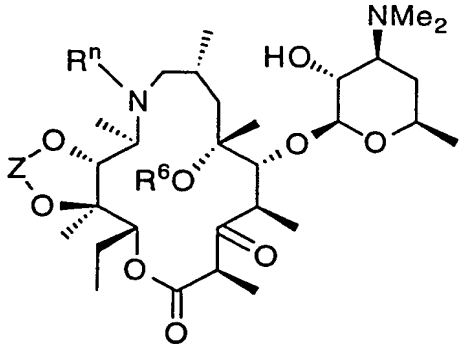
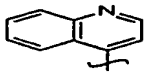
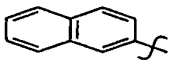
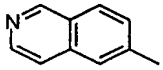
15	$(CH_2)_4Ar$	CH_3	OH	H	
16	$(CH_2)_4SO_2Ar$	CH_3	OH	H	
17	CH_3	CH_3	OH	H	------
18	$-P(O)OCH_3-$		OH	H	------
19	$-P(O)OCH_3-$		OH	H	------
20	$-COCH_2-$		OH	H	------
21	$-COCH_2-$		OH	H	------

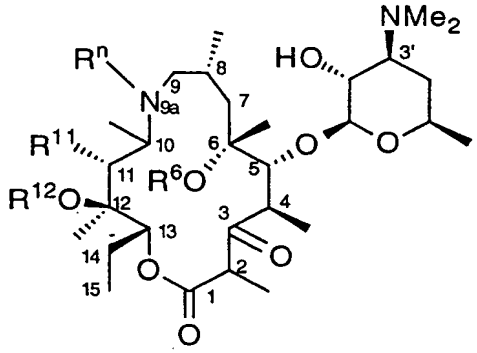
Table 3



#	Z	Rn	R6	Ar
22	$C{=}N(CH_2)_3Ar$	CH_3	CH_3	

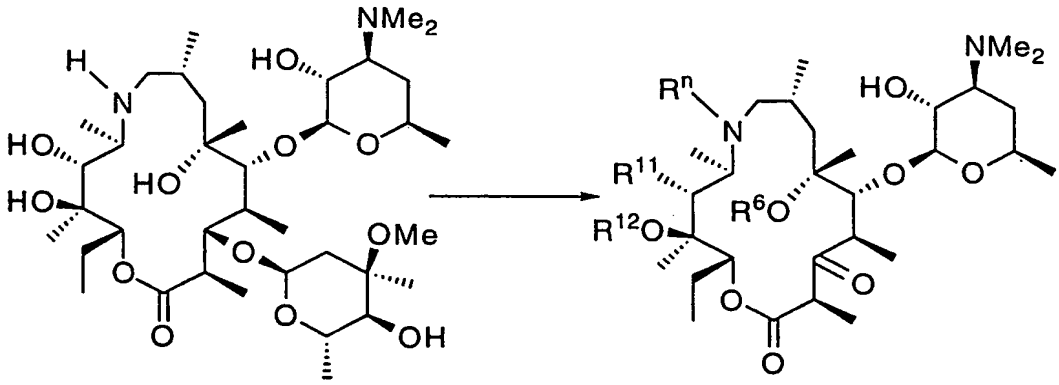
23	P(O)O(CH2)3Ar	CH3	CH3	
24	P(O)NH(CH2)3Ar	CH3	CH3	

Numbering of the 9a-aza-3-ketolides described herein is in accordance with the following scheme.



The compounds of the present invention are prepared from 9a-aza-9-deoxo-9a-homo-erythromycin A by a variety of synthetic routes. The process is illustrated by the following generic scheme:

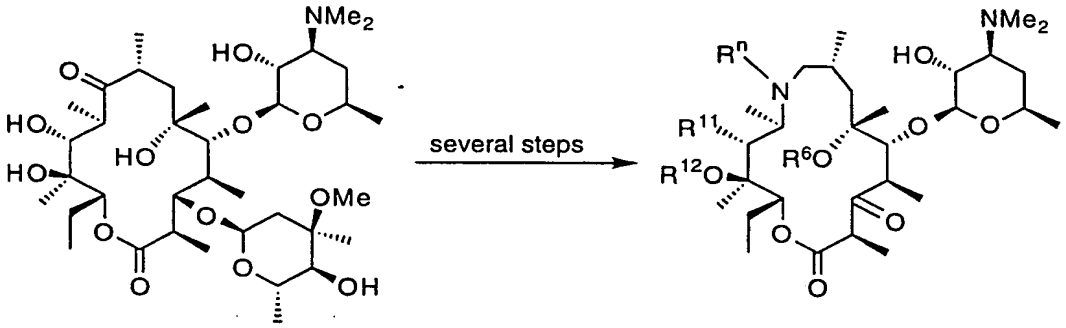
Scheme A



With reference to Scheme A, X, R^6, R^n, R^{11}, and R^{12}, are as defined with respect to the compounds of formula I.

Since 9a-aza-9-deoxo-9a-homo-erythromycin A is prepared from erythromycin, the compounds of the present invention are ultimately derived from erythromycin as shown in Scheme B. It will be further recognized that the the compounds of the present invention can be prepared from erythromycin without proceeding through the azalide intermediate shown above by simply altering the order of the steps described herein for the conversion of that intermediate to the compounds of the present invention and the steps required to introduce the 9a nitrogen.

Scheme B



At some point during the synthetic sequence, it is necessary to remove the cladinose attached at C-3 of the starting azalide. Depending on the exact nature of the final synthetic target, the cladinose removal may be best effected at either an early or late stage of the synthesis. This is generally accomplished by treating the macrolide with acid in either aqueous or alcoholic solution. Thus, a solution of the macrolide in an alcohol such as methanol, ethanol, or the like containing from 0.5 to 5% of a strong acid such as hydrochloric acid, sulfuric acid, or the like is stirred for 1 to 36 hours at a temperature ranging from 0°C to 30°C. Alternatively, a solution of the macrolide in a 0.1N to 1 N aqueous solution of a strong acid such as hydrochloric acid, sulfuric acid, or the like is stirred for 1 to 36 hours at a temperature ranging from about 0°C to 30°C. The reaction is worked up and the product macrolide isolated by first making the reaction mixture basic by adding

an aqueous solution of a base such as sodium hydroxide, sodium bicarbonate, potassium carbonate and the like then extracting the macrolide product with a suitable organic solvent such as chloroform, ethyl acetate, and the like. If the reaction is run in an alcoholic solvent, the extraction procedure may be improved by first concentrating the reaction mixture under vacuum, preferably after addition of aqueous base to neutralize the acid. When working in the erythromycin series (ketone at C-9, free OH group at C-6), the C-9 ketone must be protected (e.g. as an oxime) before attempting to remove the cladinose under the acidic conditions described above. In the azalide series (C-9 ketone removed with the addition of the 9a-nitrogen), no protection of a ketone at C-9 is necessary.

During alkylation of the C-3, 6, 11, or 12 hydroxyl group, it is necessary to protect the nitrogen at C-3' in order to prevent quaternization of the nitrogen. This can be accomplished by protection of the desosamine as the 2',3'-bis-CBZ derivative by using standard macrolide chemistry techniques. Alternatively, the 3'-nitrogen atom can be protected as an arylsulfonamide by N-demethylation followed by sulfonylation with an appropriate sulfonyl halide or sulfonic anhydride. It is not generally necessary to protect the 9a-nitrogen during alkylation reactions. However, protection of the 9a-nitrogen may be useful since it can alter the order of reactivity of the various hydroxyl groups to alkylation.

Some reactions, including but not limited to alkylation reactions, may also necessitate protection of other hydroxyl groups. This may be accomplished by protection as a silyl ether, an ester, a mixed carbonate, or any of a variety of hydroxyl protecting groups well-known to those skilled in the art.

Alkylation of the C-3, 6, 11, or 12 hydroxyl group may be accomplished by treating a solution of a suitably protected macrolide in a suitable solvent such as dimethylformamide, tetrahydrofuran, and the like with a strong base such as sodium hydride, potassium hexamethyldisilazide, and the like at a temperature ranging from -40°C to 25°C for 1 to 30 minutes then adding a suitable alkylating reagent such as an alkyl iodide, an alkyl bromide, an alkyl

trifluoromethanesulfonate, and epoxide, and the like and stirring the resulting reaction mixture at a temperature ranging from -40°C to 45°C for 15 minutes to 4 hours (appropriate temperature and length of time depends on the exact nature of the alkylating reagent).

Many of the compounds of the present invention contain fewer oxygen atoms attached to the macrolide ring than are present in erythromycin. Such deoxy analogs can be prepared by employing one of many deoxygenation methods for reductive removal of a hydroxyl group. For example, the hydroxyl group can be converted to a xanthate ester by reaction with a base such as sodium hydride, potassium hexamethyldisilazide, and the like in a solution of a suitable solvent such as tetrahydrofuran, ether, dioxane and the like at temperatures ranging from -20°C to 30°C for 1 to 30 minutes followed by reaction of the resulting alkoxide with excess carbon disulfide and iodomethane to form a methyl xanthate. The methyl xanthate can be purified using standard techniques or, alternatively, may be subjected to the radical deoxygenation procedure without purification. A solution of the methyl xanthate in a suitable solvent such as toluene, benzene, and the like is treated with a radical initiator such as azobis-isobutyrylnitrile (AIBN), triethylborane, and the like and an excess of a hydride source such as tributyltin hydride, triphenyltin hydride, and the like at a temperature ranging from room temperature to 125°C for 1 to 24 hours. The reaction is worked up and the product macrolide isolated using standard macrolide chemistry techniques.

In compounds containing a cyclic carbamate moiety at C-11 and C-12 of the macrolide ring, the cyclic carbamate may be introduced into the erythromycin molecule before the ring expansion and incorporation of the 9a-nitrogen using standard techniques of macrolide chemistry which have been published in the literature and are well known to those skilled in the art. Once the cyclic carbamate moiety is in place, the 9a-nitrogen may be installed using the standard ring expansion techniques which have been previously published. For compounds containing an alkyl group appended to the nitrogen of the 11,12-cyclic carbamate, the alkyl group may either be incorporated during the

construction of the cyclic carbamate or may be added to the completed cyclic carbamate via an alkylation procedure.

Alternatively, the 11,12-cyclic carbamate can be introduced at a stage in the sequence with the 9a nitrogen.

Introduction of the 3-keto group is accomplished by oxidation of a suitably protected precursor with a hydroxyl group at C-3 using one of the many methods for oxidation of secondary alcohols which are well-known to those skilled in the art. For example, a solution of the 3-hydroxy precursor compound in a suitable solvent such as dichloromethane, chloroform, dichloroethane and the like is treated with from 0.95 to 2 molar equivalents of an oxidation reagent such as pyridinium chlorochromate, pyridinium dichromate, Dess-Martin periodinane, chromic acid and the like for 0.1 to 24 hours at a temperature ranging from -40°C to 40°C. The reaction is worked up and the product macrolide isolated by simply filtering the reaction mixture through a piece of filter paper or through a plug of silica gel and evaporating the filtrate under vacuum. Alternatively, the reaction may be worked up by adding an aqueous solution of a base such as sodium hydroxide, sodium bicarbonate, potassium carbonate and the like then extracting the macrolide product with a suitable organic solvent such as chloroform, ethyl acetate, and the like. Evaporation of the organic extract under vacuum then affords the product. Alternatively, oxidation procedures commonly referred to by those skilled in the art as Moffat or Swern oxidations, which involve the use of activated DMSO reagents, may be employed for the oxidation of a 3-hyroxyl group to a 3-ketone. Oxidation using the Dess-Martin periodinane is preferred.

The synthesis of the target compound is completed by removing any protecting groups which are present in the penultimate intermediate using standard techniques which are well known to those skilled in the art. The deprotected final product is then purified, as necessary, using standard techniques such as silica gel chromatography, HPLC on silica gel or on reverse phase silica gel, and the like or by recrystallization.

The final product may be characterized structurally by standard techniques such as NMR, IR, MS and UV. For ease of

handling, the final product, if not crystalline, may be lyophilized from, e.g., benzene, tert-butanol and the like, to afford an amorphous, easily handled solid.

The compounds are useful in various pharmaceutically acceptable salt forms. The term "pharmaceutically acceptable salt" refers to those salt forms which would be apparent to the pharmaceutical chemist. i.e., those which are substantially non-toxic and which provide the desired pharmacokinetic properties, palatability, absorption, distribution, metabolism or excretion. Other factors, more practical in nature, which are also important in the selection, are cost of the raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug. Conveniently, pharmaceutical compositions may be prepared from the active ingredients in combination with pharmaceutically acceptable carriers.

Pharmaceutically acceptable salts include conventional non-toxic salts or quarternary ammonium salts formed, e.g., from non-toxic inorganic or organic acids. Non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized by conventional chemical methods. Generally, the salts are prepared by reacting the free base or acid with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid or base, in a suitable solvent or solvent combination.

The compounds of this invention may be used in a variety of pharmaceutical preparations. They may be employed in powder or crystalline form, in liquid solution, or in suspension. They may be administered by a variety of means; those of principal interest include: topically, orally and parenterally by injection.

Oral compositions may take such forms as tablets, capsules, oral suspensions and oral solutions. The oral compositions may utilize conventional formulating agents, and may include sustained release properties as well as rapid delivery forms. The preferred pharmaceutical composition is a table, capsule, suspension or solution, which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

The dosage to be administered depends to a large extent upon the condition and size of the subject being treated, the route and frequency of administration, the sensitivity of the pathogen to the particular compound selected, the virulence of the infection and other factors. Such matters are left to the routine discretion of the physician according to principles of treatment well known in the antibacterial arts.

The compositions for human delivery per unit dosage, whether liquid or solid, may contain from about 0.01% to as high as about 99% of active material, the preferred range being from about 10-60%. The composition will generally contain from about 15 mg to about 2.5 g of the active ingredient; however, in general, it is preferable to employ a dosage amount in the range of from about 25 mg to 1000 mg.

The preferred method of administration is oral.

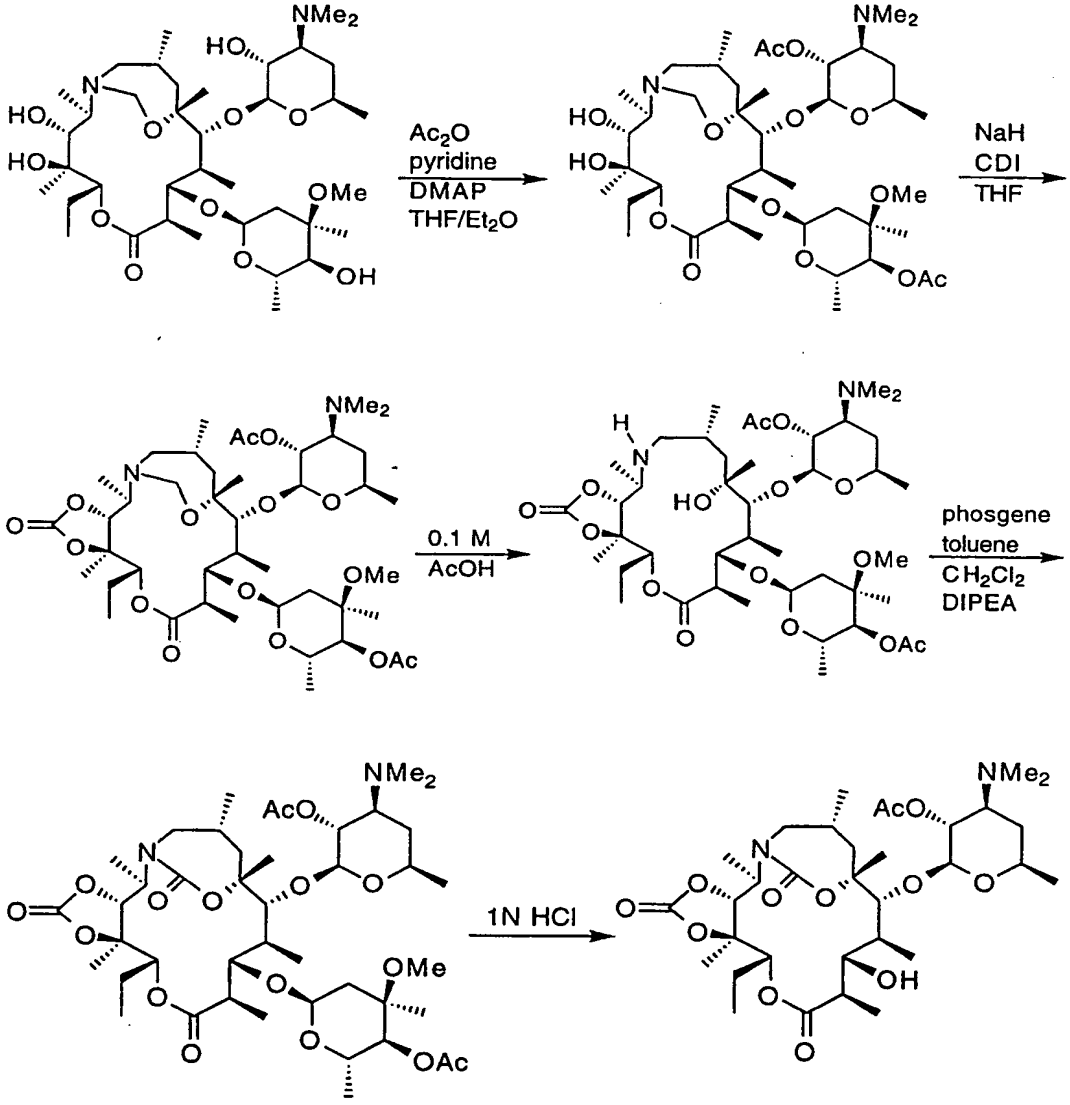
For adults, about 5-50 mg of the compound per kg of body weight given one to four times daily is preferred. The preferred dosage is 250 mg to 1000 mg of the compound given one to four times per day. More specifically, for mild infections a dose of about 250 mg two or three times daily is recommended.

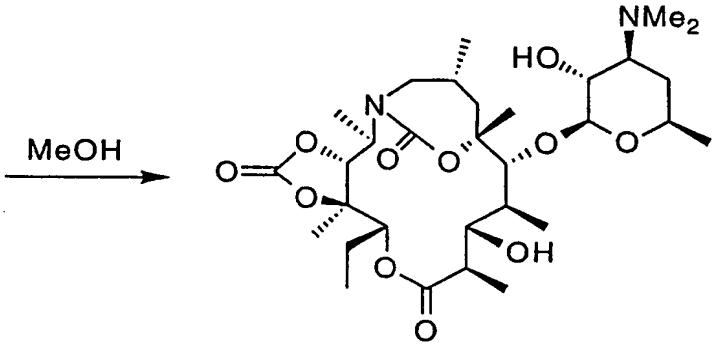
For severe infections caused by organisms at the upper limits of sensitivity to the antibiotic, a dose of about 1000-2000 mg three to four times daily may be recommended.

For children, a dose of about 5-25 mg/kg of body weight given 2, 3, or 4 times per day is preferred; a dose of 10 mg/kg may be recommended.

EXAMPLE 1

9-Deoxo-9a-aza-3-descladinosyl-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate





Step 1: 2',4"-bis(O-Acetyl)-9-deoxo-9a-aza-9a-N,6-O-methylene-9a-homoerythromycin A

A solution of 9-deoxo-9a-aza-9a,6-O-methylene-9a-homoerythromycin A (3.07 g, 4.1 mmol), 4-dimethylaminopyridine (125 mg, 1.02 mmol), and pyridine (3.5 mL, 43.3 mmol) in 5:1 ether:tetrahydrofuran (135 mL) is cooled to 0°C with stirring. Acetic anhydride (3.9 mL, 41.3 mmol) is added dropwise. The cooling bath is thereafter removed and the reaction allowed to stir at room temperature. The reaction is partitioned between ethyl acetate and saturated aqueous potassium carbonate. The organic layer is washed with brine, dried (anhydrous sodium sulfate), filtered, and evaporated to give the title compound.

Step 2: 2',4"-bis(O-Acetyl)-9-deoxo-9a-aza-9a,6-O-methylene-9a-homoerythromycin A 11,12-carbonate

A solution of 2',4"-bis(O-acetyl)-9-deoxo-9a-aza-9a,6-O-methylene-9a-homoerythromycin A (1.0 g, 1.2 mmol) in anhydrous tetrahydrofuran (7 mL) is stirred at room temperature as sodium hydride (104 mg of 60% dispersion in mineral oil, 2.6 mmol) is added. 1,1'-Carbonyldiimidazole (0.88 g, 5.4 mmol) is then added with further stirring at 70°C. Saturated aqueous sodium bicarbonate is added dropwise. The aqueous layer is extracted twice with ethyl acetate. The combined organic layers are washed with 5% aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, filtered, and evaporated to give the title compound.

Step 3: 2',4"-bis(O-Acetyl)-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate

A solution of 0.1 M aqueous acetic acid (250 mL) is added to 2',4"-bis(O-acetyl)-9-deoxo-9a-aza-9a,6-O-methylene-9a-homoerythromycin A 11,12-carbonate (1.09 g, 1.2 mmol). The resulting suspension is stirred at room temperature for 8 hours. The aqueous layer is washed with ethyl acetate (5 mL). The aqueous layer is made basic by the dropwise addition of saturated aqueous potassium carbonate and extracted with ethyl acetate (2 x 250 mL). The combined organic layers are washed with brine, dried over anhydrous potassium carbonate, and evaporated to give the title compound.

11,12-carbonate-9a-N,-6-O-carbamate

A solution of 2',4"-bis(O-acetyl)-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate (0.86 g, 1.02 mmol) and 4-dimethylaminopyridine (32.4 mg, 0.27 mmol) in dichloromethane (8 mL) is stirred under a nitrogen atmosphere. N,N-Diisopropylethylamine (8.0 mL, 45.9 mmol) is added followed by the dropwise addition of phosgene (20% in toluene, 8.0 mL, 20.3 mmol). The reaction is stirred at room temperature, and partitioned between dichloromethane and saturated aqueous potassium carbonate. The organic layer is washed with water, dried (anhydrous potassium carbonate), filtered, and evaporated to give the title compound.

Step 5: 2'-O-Acetyl-3-descladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate

A solution of 2',4"-bis(O-acetyl)-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,6-O-carbamate(1.29 g) in 0.86M aqueous hydrochloric acid (350 mL) is stirred at room temperature to completion. The solution is made basic with saturated aqueous potassium carbonate and extracted with ethyl acetate (3 x 300 mL). The combined organic layers are washed with brine, dried (anhydrous sodium sulfate), filtered, and evaporated to produce the crude product.

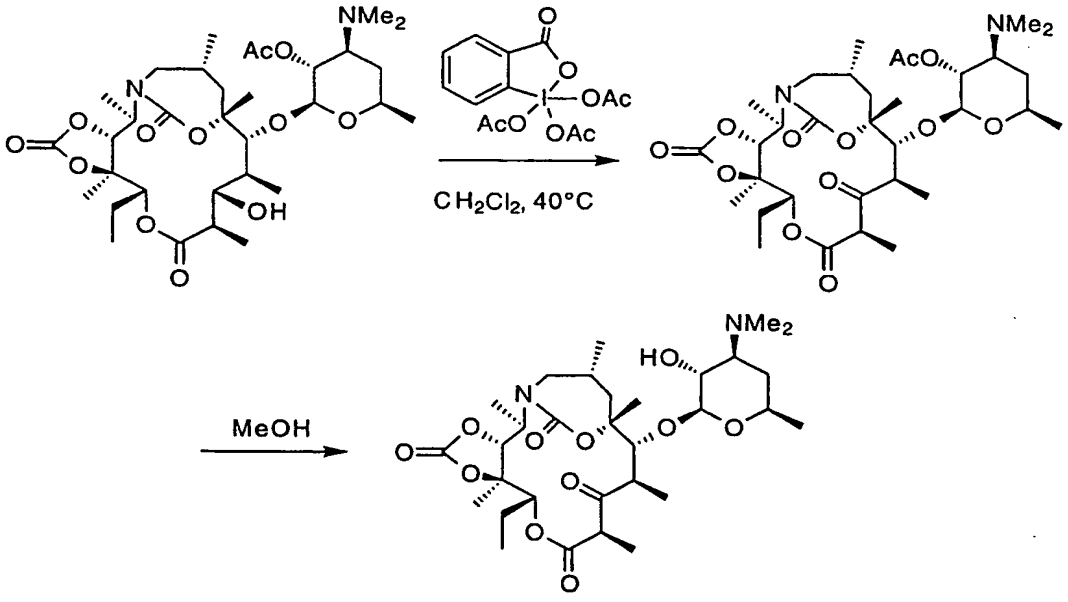
The crude solid is dissolved in 2:1 hexane:acetone and loaded onto a silica gel column (2.75 cm dia., 22 g of silica, 20 mL fractions), eluted with the same solvent system. The appropriate fractions can be combined, evaporated, and lyophilized (from benzene) to give the title compound.

Step 6: 3-descladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate

A solution of 2'-O-acetyl-9-deoxo-9a-aza-9a,6-O-carbonyl-11-O,12-O-carbonyl-3-descladinosyl-9a-homoerythromycin A (11.1 mg, 0.017 mmol) is stirred in methanol (3 mL). The solvent is evaporated and the residue lyophilized (from benzene) to give the title compound.

EXAMPLE 2

3-descladinosyl-3-oxo-9-Deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate



Step 1: 2'-O-Acetyl-3-descladinosyl-3-oxo-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate

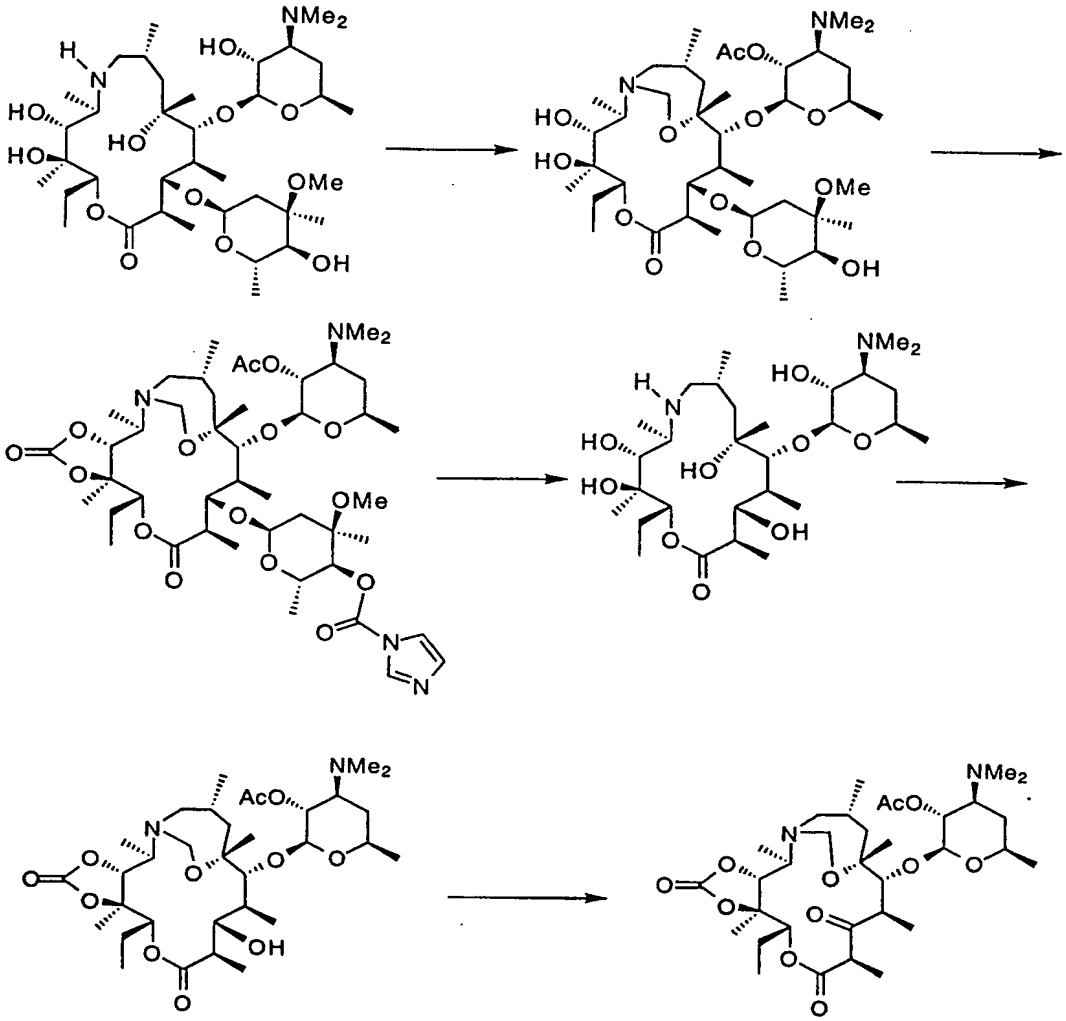
A solution of Dess-Martin periodinane (200.1 mg, 0.47 mmol) and 2'-O-acetyl-3-descladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate (50.8 mg, .076 mmol) in dichloromethane (3 mL) is stirred at reflux for 90 minutes. The reaction mixture is partitioned between dichloromethane and saturated aqueous potassium carbonate, the layers separated, and the organic layer washed with water (10 mL), dried (anhydrous potassium carbonate), filtered, and evaporated. The residue is dissolved in 1:1 dichloromethane:ether (20 mL). A solution containing sodium bicarbonate (1.3 g) and sodium thiosulfate (4.6 g) in water (15 mL) is added. Saturated sodium bicarbonate is added and the layers are separated. The combined organic layers are dried over anhydrous sodium sulfate, filtered and evaporated. The product is combined with 2:1 hexane:acetone, loaded onto a 2 x 14.5 cm silica gel column and was eluted with 2:1 hexane:acetone. The appropriate fractions are combined and evaporated to give the title compound.

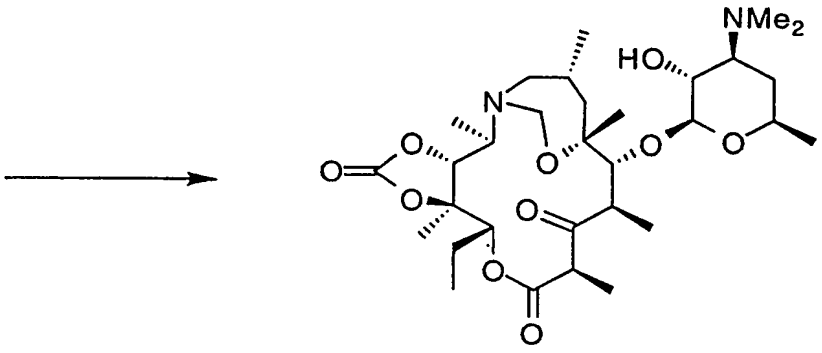
Step 2: 3-descladinosyl-3-oxo-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate

A solution of 2'-O-acetyl-3-descladinosyl-3-oxo-9-deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate in methanol (5 mL) is stirred at room temperature. The solvent is evaporated and the residual solid lyophilized from benzene to give the title compound.

EXAMPLE 3

3-descladinosyl-3-oxo-9-deoxo-9a-aza-9a-N,6-O-methylene-9a-homoerythromycin A 11,12-carbonate





Step 1: 2'-O-acetyl-9a-N,6-O--methylene-9-deoxo-9a-aza-9a-homoerythromycin A

To a solution of 2.98 g of 9-deoxo-9a-aza-9a-homoerythromycin A in 70 mL of chloroform is added 0.750 mL of 37% aq. formaldehyde. The mixture is refluxed for 1.5 hours, after which time the reaction is diluted with 150 mL chloroform and extracted with 50 mL of sat. aq. potassium carbonate. The organic layer is separated, dried over anhydrous potassium carbonate, and the solvent removed under reduced pressure. The crude residue is dissolved in 20 mL of 1:1 ethyl acetate:methylene chloride. 0.800 mL of acetic anhydride is added, and the mixture is stirred at room temperature for 1.5 hours. The solvent is removed under reduced pressure to afford the title compound.

Step 2: 2'-O-acetyl-9a-N,6-O--methylene-9-deoxo-9a-aza-9a-homoerythromycin A-4"-imidazoylcarbamate-11,12 carbonate

To a solution of 0.103 g (0.127 mmol) of 2'-O-acetyl-aa-N,6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A in 1.0 mL of tetrahydrofuran is added 0.103 g of carbonyldiimidazole (5 eq.), then 12.7 mg of sodium hydride (60% oil dispersion). The mixture is refluxed for 25 minutes. The reaction is diluted with 50 mL ethyl acetate and washed three times with 10 mL of sat. aq. sodium bicarbonate. The organic layer is separated, dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure to afford the title compound.

Step 3: 2'-O-acetyl-3-descladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A-11,12 carbonate

A solution of 0.110 g (0.127 mmol) of 2'-O-acetyl-9a-N,6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A-4"-imidazoylcarbamate-11,12 carbonate in 5.0 mL of 0.25 N aq. HCl is allowed to stir at room temperature for 12 hours. The reaction is diluted with 50 mL ethyl acetate and washed three times with 30 mL of sat. aq. sodium bicarbonate. The organic layer is separated, dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure to afford the title compound.

Step 4: 2'-O-acetyl-3-descladinosyl-9a-N,6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A-11,12 carbonate

To a solution of 0.074 g (0.122 mmol) of 2'-O-acetyl-3-descladinosyl-9-deoxo-9a-aza-9a-homoerythromycin A-11,12 carbonate in 2.0 mL of chloroform is added 0.050 mL of 37% aq. formaldehyde. The mixture is refluxed for 1 hour, after which time the reaction is diluted with 150 mL chloroform and extracted with 50 mL of sat. aq. potassium carbonate. The organic layer is separated, dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure to afford the title compound.

Step 5: 2'-acetoxy-3-descladinosyl-3-oxo-9a-N,6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A-11,12 carbonate

To a solution of 0.158 g of 2'-O-acetyl-3-descladinosyl-9a-N,6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A-11,12 carbonate in 1.6 mL of chloroform is added 158 mg of the Dess-Martin periodinane reagent. The mixture is stirred at room temperature for 35 minutes, after which time the reaction is diluted with 30 mL chloroform and 30 mL of saturated aqueous sodium bicarbonate. The organic layer is separated and the aqueous layer is back extracted with 15 mL of methylene chloride. The combined organics are dried over anhydrous potassium carbonate, and the solvent is removed under reduced pressure. The crude material is chromatographed on silica gel eluted

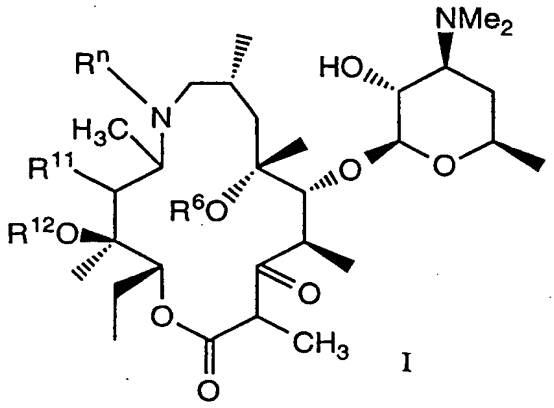
with 1:1 hexane:acetone. The fractions containing the desired product are combined and evaporated to afford the title compound.

Step 6: 3-descladinosyl-3-oxo-9a-N,6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A-11,12 carbonate

A solution of 0.035 g of 2'-O-acetyl-3-descladinosyl-3-oxo-9a-N,6-O-methylene-9-deoxo-9a-aza-9a-homoerythromycin A-11,12 carbonate in 2.0 mL of methanol is stirred at room temperature for 5.5 hours, after which time the solvent is removed under reduced pressure. The crude material is chromatographed on silica gel eluting with 1:4 hexane:acetone. The fractions containing the desired product are combined and evaporated to afford the title compound.

WHAT IS CLAIMED IS:

1. A compound represented by formula I:



I

or a salt or hydrate thereof wherein:

R^{11} and R^{12} are taken separately or together;

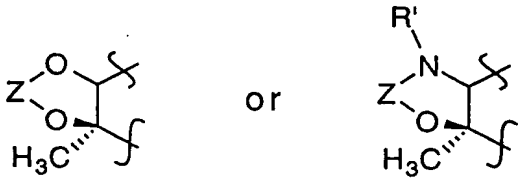
when taken separately, R^{11} is selected from the group consisting of: NR'R", $O(CH_2)_nAr$ and $S(CH_2)_nAr$;

and R^{12} represents a member selected from the group consisting of: H, C_{1-6} alkyl, uninterrupted or interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups, and $(CH_2)_nAr$ wherein

$(CH_2)_n$ is alkylene, in which n is an integer of from 1 to 10, uninterrupted or interrupted by 1-3 of O, $S(O)_y$ wherein y is 0, 1 or 2, NH, NCH_3 or C(O), and unsubstituted or substituted with 1-3 R^a groups;

and Ar represents a 5-10 membered monocyclic or bicyclic aromatic ring system containing from 0-3 heteroatoms, which are selected from O, $S(O)_y$ and N, unsubstituted or substituted with from 1-3 groups R^a which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2, C_{1-3} alkyl, and when two R^a groups are present, said two substituents may be taken in combination with any intervening atoms to represent a 5-6 membered ring, aromatic or non-aromatic, optionally containing 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

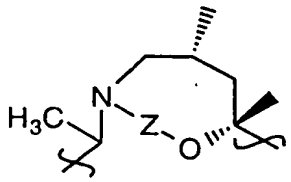
when taken together, R^{11} and R^{12} taken with the intervening atoms form an additional ring as shown in the following structure:



wherein R' and Z are as defined below;

R^n represents H, C_{1-6} alkyl, C_{1-6} alkyl interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O), unsubstituted or substituted with 1-3 R^a groups, or $(CH_2)_nAr$ wherein $(CH_2)_n$ and Ar are as defined above, and R^6 represents H or CH_3,

or R^6 and R^n are taken in conjunction with the intervening atoms and form an additional ring as shown in the following structure:



Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2;

X represents CH_2 , CHF, CF_2, $C=CH_2$, CHSR, $CHCH_3$, C=S, C=O or CHOR;

R represents H, CS_2CH_3, phenyl, C_{1-6} alkyl or C_{1-6} alkyl interrupted by 1-3 of O, $S(O)_y$, N, NH, NCH_3 or C(O);

R^z represents C_{1-6} alkyl or phenyl;

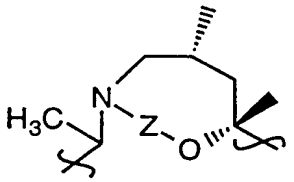
R' is selected from H, C_{1-3} alkyl, NHR"and $(CH_2)_nAr$, and

R" represents H, C_{1-3} alkyl or $(CH_2)_nAr$.

2. A compound in accordance with claim 1 wherein R^n represents H, C_{1-6} alkyl, C1-6 alkyl substituted with 1-3 R^a groups or $(CH_2)_nAr$.

3. A compound in accordance with claim 1 wherein R^6 represents CH_3.

4. A compound in accordance with claim 1 wherein R^6 and R^n taken together with the intervening atoms form a ring as shown in the following structure:



in which Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

5. A compound in accordance with claim 1 wherein Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl.

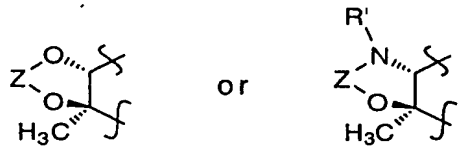
6. A compound in accordance with claim 1 wherein $(CH_2)_nAr$ is present, and $(CH_2)_n$ is uninterrupted, and n is an integer of from 1-3, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl.

7. A compound in accordance with claim 1 wherein R^{11} and R^{12} are taken separately, and R^{11} is selected from the group

consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined.

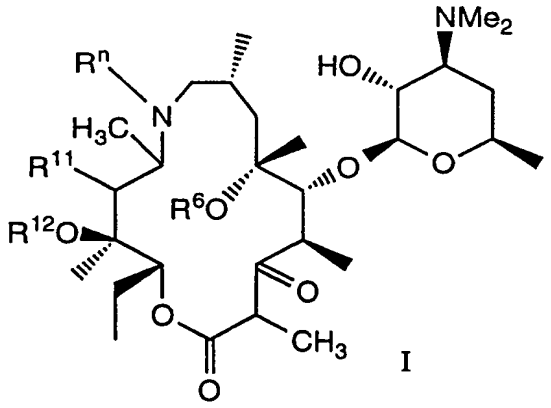
8. A compound in accordance with claim 1 wherein R^{11} and R^{12} are taken separately, and R^{12} represents H, C_{1-6} alkyl or $(CH_2)_n$-Ar.

9. A compound in accordance with claim 1 wherein R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring as shown in the following structure:



wherein Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO or CH_2XCH_2 wherein R', R" and X are as originally defined.

10. A compound represented by formula I:

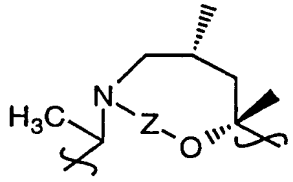


I

or a pharmaceutically acceptable salt or hydrate thereof, wherein:

R^6 represents CH_3;

or R^6 and R^n are taken together with the intervening atoms to form a ring as shown in the following structure:



in which Z represents CH_2, C(O), C(NR"), P(O)OR", P(O)NR^nR", $Si(R^z)_2$, SO, SO_2, CH_2CO, $COCH_2$, $COCH_2CH_2$, CH_2CH_2CO, CH_2CH_2 or CH_2XCH_2 wherein R', R" and X are as originally defined;

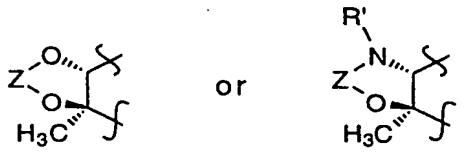
Ar represents a monocyclic or bicyclic aromatic ring system containing from 0-2 heteroatoms, which are selected from O, S and N, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

$(CH_2)_n$ represents an alkylene chain which is uninterrupted, and n is an integer of from 1-3, unsubstituted or substituted with from 1-3 R^a groups which are selected from halo, OH, OMe, NO_2, NH_2, CN, SO_2NH_2 and C_{1-3} alkyl;

R^{11} and R^{12} are taken separately, and R^{11} is selected from the group consisting of: OH and $O(CH_2)_nAr$, in which $(CH_2)_n$ and Ar are as previously defined, and

R^{12} represents H, C1-6 alkyl or (CH2)n-Ar, or

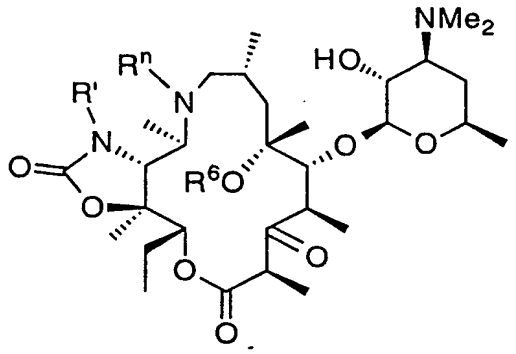
R^{11} and R^{12} are taken together with the intervening atoms and form an additional ring as shown in the following structure:

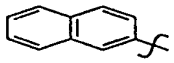
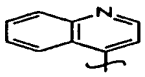
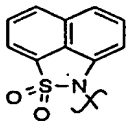
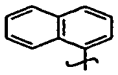
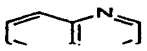


wherein Z is as originally defined.

11. A compound in accordance with claim 1 falling within one of the following tables:

Table 1



#	Rn	R6	R'	Ar
1	CH3	CH3	(CH2)4Ar	
2	CH3	CH3	(CH2)4Ar	
3	CH3	CH3	$(CH_2)_5Ar$	
4	CH3	CH3	(CH2)3Ar	
5	CH3	CH3	(CH2)4Ar	
				

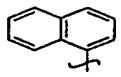
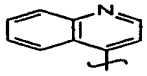
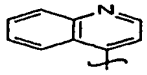
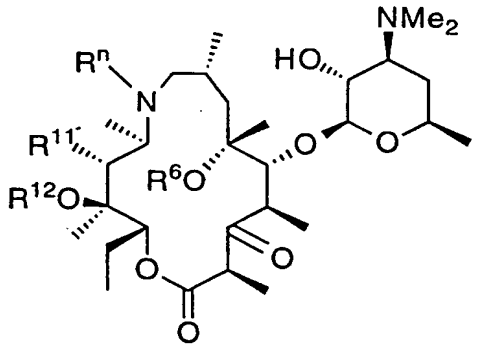
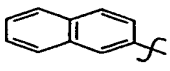
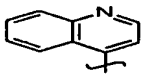
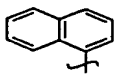
7	---CH_2---		$(CH_2)_4Ar$	
8	---CH_2---		$NH(CH_2)_3Ar$	
9	CH_3	CH_3	$NH(CH_2)_3Ar$	

Table 2



#	R^n	R^6	R^{11}	R^{12}	Ar
10	CH_3	CH_3	$O(CH_2)_3Ar$	H	
11	CH_3	CH_3	OH	$(CH_2)_3Ar$	
12	CH_3	CH_3	$O(CH_2)_3Ar$	H	
13	CH_3	CH_3	$O(CH_2)_4Ar$	H	

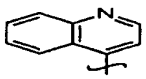
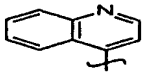
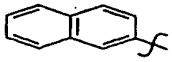
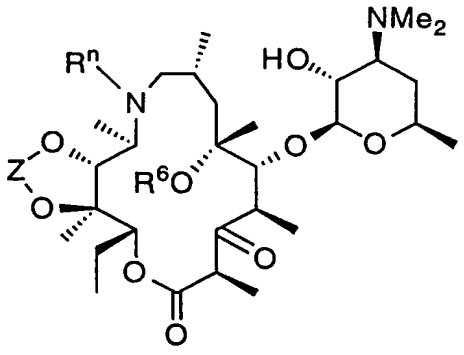
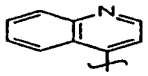
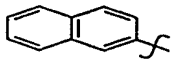
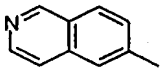
14	CH_3	CH_3	$S(CH_2)_4Ar$	H	
15	$(CH_2)_4Ar$	CH_3	OH	H	
16	$(CH_2)_4SO_2Ar$	CH_3	OH	H	
17	CH_3	CH_3	OH	H	------
18	$-P(O)OCH_3-$		OH	H	------
19	$-P(O)OCH_3-$		OH	H	------
20	$-COCH_2-$		OH	H	------
21	$-COCH_2-$		OH	H	------

Table 3



22	C=N(CH2)3Ar	CH3	CH3	
23	P(O)O(CH2)3Ar	CH3	CH3	
24	P(O)NH(CH2)3Ar	CH3	CH3	

12. A compound in accordance with claim 1 having the name:

3-descladinosyl-3-oxo-9-Deoxo-9a-aza-9a-homoerythromycin A 11,12-carbonate-9a-N,-6-O-carbamate or

3-descladinosyl-3-oxo-9-deoxo-9a-aza-9a-N,6-O-methylene-9a-homoerythromycin A 11,12-carbonate.

13. A pharmaceutical composition which is comprised of a compound of formula I in combination with a pharmaceutically acceptable carrier.

14. A method of treating a bacterial infection in a mammalian patient in need of such treatment which is comprised of administering to said patient a compound of formula I in an amount which is effective for treating a bacterial infection.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13061

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/33, 31/70; C07D 267/00; C07H 5/04, 5/06, 17/08
US CL :514/183; 536/7.1, 7.2, 7.3, 7.4; 540/467, 468
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/183; 536/7.1, 7.2, 7.3, 7.4; 540/467, 468

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 691 464 A1 (ROUSSEL-UCLAF) 26 November 1993, especially page 10.	1-3, 8, 10, 11, 13 and 14
Y	EP 0 283 055 A2 (SOUR PLIVA FARMACEUTSKA) 21 September 1988, see entire document.	1-3, 8, 10, 11, 13 and 14
Y	DJOKIC et al., Erythromycin Series. Part 13. Synthesis and Structure Elucidation of 10-Dihydro-10-deoxo-11-methyl-11-azaerythromycin A. Journal of Chemical Research. May 1988, No. 5, pages 152-153, especially page 152.	1-3, 8, 10, 11, 13 and 14

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 25 SEPTEMBER 1998	Date of mailing of the international search report 29 OCT 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer MUKUND SHAH Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/13061

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DJOKIC et al. Erythromycin Series. Part 11. Ring Expansion of Erythromycin A Oxime by the Beckmann Rearrangement. Journal of the Chemical Society, Perkin Trans I. 1986, No. 11, pages 1881-1890, especially page 1887.	1-3, 8, 10, 11, 13 and 14